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Review Article

Differential diagnosis of POLG related disorders: What to keep in mind when multiorgan system is involved?

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Abstract

Mitochondrial and lysosomal dysfunction accounts for a large group of inherited metabolic disorders most of which are due to a dysfunctional mitochondrial respiratory chain (MRC) leading to deficient energy production and defects in phagocytosis in endosomal-lysosomal pathway respectively. MRC function depends on the coordinated expression of both nuclear (nDNA) and mitochondrial (mtDNA) genomes. Thus, mitochondrial diseases can be caused by genetic defects in either the mitochondrial or the nuclear genome, or in the cross-talk between the two. The mitochondrial DNA depletion syndromes (MDSs) are a clinically heterogeneous group of disorders with an autosomal recessive pattern of inheritance that have onset in infancy or early childhood and are characterized by a reduced number of copies of mtDNA in affected tissues and organs. In this review article, we summarized the spectrum of mtDNA depletion disorders along with minor learning of lysosomal storage diseases. This current article offers a perspective on the role of genetics in medical practice and how this role may evolve over the next several years.

Introduction

The polymerase gamma (POLG) gene (POLG1) is located on the long arm of chromosome 15 and encodes for alpha subunit DNA polymerase γ, while the POLG2 gene, located on the long arm of chromosome 17, encodes for its catalytic accessory subunit. Pol γ functions in mitochondria. Uncontrolled mtDNA defects may result from damage to either of these two genes causing variable phenotypic features across ones' lifespan [1-3].

Mutations in POLG can cause early childhood mito-chondrial DNA (mtDNA) depletion syndromes or later- onset syndromes arising from mtDNA deletions. It is very rare with an incidence of approximately 1 in 50000 people [4]. In several cases a family history of mitochondrial disorder is not found [1,2]. Mutations in POLG1 are inherited in autosomal recessive pattern whereas mutations in POLG2 can only lead to autosomal dominant progressive external ophthalmoplegia [1-3].

It ranges from myocerebrohepatopathy spectrum in infancy to parkinsonism in elderly. Six most common disorders are Alpers-huttenlocher syndrome (AHS), childhood myocerebrohepatopathy spectrum (MCHS), myoclonic epilepsy myopathy sensory ataxia (MEMSA), ataxia neuropathy spectrum (ANS), autosomal recessive progressive external ophthalmoplegia (arPEO), autosomal dominant progressive external ophthalmoplegia (adPEO) [5]. Apart from the abovementioned disorders, there are several other diseases that are associated with mtDNA depletion with multiorgan presentation.

Disorders to consider

1) Epilepsia partialis continua (EPC): It is seen in

Alpers-Huttenlocher syndrome (AHS) [6], and also can result from structural brain lesions (e.g., stroke, neoplasia, cortical dysplasia, traumatic lesion etc.). EPC has also been described in individuals with COQ8A-related primary coenzyme Q10 deficiency [7], NADH coenzyme Q reductase deficiency [8], MERRF, Leigh syndrome, and nonketotic hyperglycemia [9]. Recently, biallelic TBC1D24 pathogenic variants were identified in an individual with EPC [10].

2) Mitochondrial DNA Depletion (MDD) Disorders: MDD disorders may affect either a specific tissue (most commonly muscle or liver) or multiple organs, including the heart, brain, and kidney. MDD disorders need to be distinguished from the disorders of mtDNA mutation, duplication, or deletion. Mitochondrial DNA depletion syndromes, a genetically and clinically heterogeneous group of autosomal recessive disorders, are characterized by a severe reduction in mtDNA content leading to impaired energy production in affected tissues and organs.

Mitochondrial DNA depletion syndromes occur as a result of defects in mtDNA maintenance caused by pathogenic variants in nuclear genes that function in either mitochondrial nucleotide synthesis (e.g., TK2, SUCLA2, SUCLG1, RRM2B, DGUOK, and TYMP) or mtDNA replication(e.g., POLG and TWNK) [11,12]. Mitochondrial DNA depletion syndromes are phenotypically classified into myopathic, encephalomyopathic, hepatocerebral, and neurogastrointestinal forms [13].

Myopathic forms present in infancy or early childhood with hypotonia, proximal muscle weakness, dysarthria, feeding difficulty, and failure to thrive. Cognition is usually spared in this prototype. Typically, there is rapid progression of muscle weakness with respiratory failure and death within a few years of onset. Genes associated with this form are TK2 [14], RRM2B (p53R2) [15], DGUOK (dGK) [16].

Encephalomyopathic mtDNA depletion syndromes usually presents in infancy with hypotonia, muscle weakness, psychomotor delay, sensorineural hearing impairment, lactic acidosis, and neurological dysfunction. Closely associated genes are RRM2B (p53R2) [17], TK2 [18], SUCLA2 [19], SUCLG1 [20].

Hepatocerebral forms present in neonatal and early childhood associated with hepatic dysfunction, psychomotor delay, hypotonia, lactic acidosis, nystagmus, neurological dysfunction. Genes associated are C10orf2 (Twinkle/PEO1) [21], DGUOK (dGK) [22], MPV17 (SYM1) [23], TK2 [24].

Neurogastrointestinal forms, the prototype of which is mitochondrial neurogastrointestinal encephalopathy (MNGIE) disease, may present in adolescence to early adulthood with progressive gastrointestinal dysmotility, cachexia, and peripheral neuropathy, ptosis, and neurological dysfunction. Genes associated are TYMP (ECGF1) [25], RRM2B (p53R2) [26],

a) Deoxyguanosine kinase deficiency (DGUOK deficiency): The two forms of DGUOK deficiency are a hepatocerebral mtDNA depletion syndrome (multisystem disease in neonates) and isolated hepatic disease later in infancy or childhood. The majority of affected individuals have the multisystem illness with hepatic disease (jaundice, cholestasis, and elevated transaminases) and neurologic manifestations (hypotonia, nystagmus, and psychomotor retardation) evident within weeks of birth. In contrast to AHS caused by POLG pathogenic variants, DGUOK deficiency is not characterized by seizures or brain imaging abnormalities [27].

Those with isolated liver disease may also have renal involvement and some later develop mild hypotonia. Progressive hepatic disease is the most common cause of death in both forms. Reduced mtDNA copy number in liver or muscle can be used to confirm mtDNA depletion. Molecular genetic testing of DGUOK is necessary to establish the specific diagnosis of DGUOK deficiency [22].

b) MPV17-related hepatocerebral mtDNA depletion syndrome (Navajo neurohepatopathy): It is characterized by liver failure, severe sensory neuropathy, corneal anesthesia and scarring, cerebral leukoencephalopathy, failure to thrive, and metabolic acidosis. Homozygosity for the MPV17 pathogenic variant NP_002428.1: p. Arg50Gln (NM_002437.4: c.149G>A) is associated with Navajo neurohepatopathy, a mtDNA depletion syndrome displaying hepatic failure early in life, prevalent in the Navajo tribes in the southwestern United States and Mexico [28-30].

c) SUCLA2-related mtDNA depletion syndrome, encephalomyopathic form with methylmalonic aciduria: SUCLA2-related mitochondrial DNA (mtDNA) depletion syndrome, encephalomyopathic form with methylmalonic aciduria is characterized by onset of the following features in infancy or childhood (median age of onset 2 months; range of onset birth to 6 years): psychomotor retardation, hypotonia, dystonia, muscular atrophy, sensorineural hearing impairment, postnatal growth retardation, and feeding difficulties.

Other, less frequent features include distinctive facial features, contractures, kyphoscoliosis, gastroesophageal reflux, ptosis, choreoathetosis, ophthalmoplegia, and epilepsy (infantile spasms or generalized convulsions). The median survival is 20 years; approximately 30% of affected individuals succumb during childhood. Affected individuals may have hyperintensities in the basal ganglia, cerebral atrophy, and leukoencephalopathy on head MRI. Elevation of methylmalonic acid (MMA) in the urine and plasma is found in a vast majority of affected individuals, although at levels that are far below those typically seen in individuals with classic methylmalonic aciduria [31].

d) FBXL4-related encephalomyopathic mtDNA depletion syndrome: It is a multisystem disorder

characterized primarily by congenital or early-onset lactic acidosis and growth failure, feeding difficulty, hypotonia, and global developmental delay. Other neurologic manifestations can include seizures, movement disorders, ataxia, autonomic dysfunction, and stroke-like episodes. All affected individuals alive at the time they were reported (median age: 3.5 years), demonstrated significant global developmental delay.

Other findings can involve the heart (hypertrophic cardiomyopathy, congenital heart malformations, arrhythmias), liver (mildly elevated transaminases), eyes (cataract, strabismus, nystagmus, optic atrophy), hearing (sensorineural hearing loss), and bone marrow (neutropenia, lymphopenia). Survival varies; the median age of reported deaths was two years (range 2 days - 75 months), although surviving individuals as old as 36 years have been reported. To date FBXL4-related mtDNA depletion syndrome has been reported in 50 individuals [32].

e) SUCLG1-related mtDNA depletion syndrome, encephalomyopathic form with methylmalonic aciduria: It is characterized in the majority of affected newborns by hypotonia, muscle atrophy, feeding difficulties, and lactic acidosis. Affected infants commonly manifest developmental delay, cognitive impairment, growth retardation, failure to thrive, hepatopathy, sensorineural hearing impairment, dystonia, and hypertonia.

Notable findings in some affected individuals include hypertrophic cardiomyopathy, epilepsy, myoclonus, microcephaly, sleep disturbance, rhabdomyolysis, contractures, hypothermia, and/or hypoglycemia. Life span is shortened, with median survival of 20 months. The phenotype may be indistinguishable from SUCLA2-related mtDNA depletion syndrome, encephalomyopathic form, with mild methylmalonic aciduria. Affected individuals have urinary excretion of MMA, combined respiratory chain enzyme deficiency, and mtDNA depletion [33].

f) RRM2B-related mitochondrial disease: Mutation of RRM2B has been associated with severe muscle mtDNA depletion in several families. This disorder manifests as severe encephalopathy, myopathy with persistent lactic acidosis, hypotonia, renal tubular defects, seizures, and diarrhea. Death has been reported to occur by age four months, but affected individuals have demonstrated longer survival [34].

g) Mitochondrial neuro-gastrointestinal encephalopathy (MNGIE): It is characterized by progressive gastrointestinal dysmotility (manifesting as early satiety, nausea, dysphagia, gastroesophageal reflux, postprandial emesis, episodic abdominal pain and/or distention, and diarrhea), cachexia, ptosis/ophthalmoplegia or ophthalmoparesis, leukoencephalopathy, demyelinating peripheral neuropathy, and symmetric and distal weakness more prominently affecting the lower extremities.

The order in which manifestations appear is unpredictable. Onset is usually between the first and fifth decade in about 60% of individuals and symptoms begin before 20 years. The diagnosis of MNGIE disease can be established in a proband by detection of one of the following: biallelic pathogenic variants in TYMP; markedly reduced levels of thymidine phosphorylase enzyme activity; and elevated plasma concentrations of thymidine and deoxy-uridine [35-38].

h) TK2-related mtDNA depletion syndrome: Mitochondrial myopathy with mtDNA depletion is caused by pathogenic variants in TK2. The clinical spectrum of TK2 mutations is not limited to severe infantile myopathy with motor regression and early death but includes spinal muscular atrophy type 3-like presentation, rigid spine syndrome, and subacute myopathy without motor regression and with longer survival [39-41].

3) MGME1-related mtDNA depletion syndrome 11: It is caused by biallelic pathogenic variants in MGME1. Individuals present between ages 10 and 36 years with ptosis, followed by mild PEO, diffuse skeletal muscle wasting and myopathy, profound emaciation, and respiratory failure. Intellectual disability was found in only one family of three affected individuals [42,43].

4) SLC25A4-related mtDNA depletion syndrome 12B, cardiomyopathic type: It is caused by biallelic pathogenic variants in SLC25A4. Affected individuals may present with the SANDO phenotype which may include sensory ataxic neuropathy, dysarthria, and ophthalmoparesis [40].

5) Other disorders to consider:

a) Leigh syndrome: It is a progressive neurodegenerative disorder characterized by hypotonia, spasticity, dystonia, muscle weakness, hypo- or hyperreflexia, seizures, movement disorders, cerebellar ataxia, and peripheral neuropathy. In individuals with Leigh syndrome, MRI changes most often occur initially in the brain stem and the gliosis "migrates" over time to involve the deep gray masses and cortex, whereas in AHS the initial lesions form in the cerebral cortex (usually the occipital lobes), followed by the cerebellum, basal ganglia, thalamus, and brain stem [45].

b) Autosomal dominant progressive external ophthalmoplegia: It is caused by pathogenic variants in DGUOK, DNA2, OPA1, POLG2, RNASEH1, RRM2B, TK2, or TWNK genes. Individuals with this disease may present with variable degrees of sensorineural hearing loss, generalized myopathy, depression, ataxia, parkinsonism, axonal neuropathy, cataracts, and hypogonadism [46,47].

c) Oculopharyngeal muscular dystrophy (OPMD): Disease onset is usually after 45 years and may result in progressive ptosis and bulbar dysfunction causing swallowing difficulty. This disorder may mimic the clinical manifestations

of the POLG-related disorders in which PEO is the predominant feature. OPMD is caused by pathogenic variants in PABPN1 and inherited in either an autosomal dominant or an autosomal recessive manner [48].

d) Amish lethal microcephaly: It is characterized by microcephaly and early death. The occipitofrontal circumference is typically six to 12 SD below the mean, anterior and posterior fontanels are closed at birth, and facial features are distorted. The average life span is between five and six months.

Diagnosis is based on a tenfold increase in the levels of the urinary organic acid 2-ketoglutarate. SLC25A19 is the only gene known to be associated with Amish lethal microcephaly. All affected individuals within the old order Amish population are homozygous for the same single-base pair substitution [49-51].

e) Chronic progressive external ophthalmoplegia (CPEO): In a simpler case or when there is a maternal family history can result in large-scale single deletion of mtDNA that may only be detected in limited tissues (e.g., skeletal muscle). CPEO is sometimes complicated by mild proximal muscle weakness and dysphagia, and can be considered to lie on a spectrum of disease from pure CPEO to Kearns-Sayre syndrome phenotype. Some individuals with CPEO (< 20%) have a pathogenic single-nucleotide variant of mtDNA (e.g., m.3243A>G) [48].

f) Kearns-Sayre syndrome (KSS): A mtDNA deletion syndrome, is a multisystem disorder defined by the triad of onset before age 20 years, pigmentary retinopathy, and progressive external ophthalmoplegia (PEO). In addition, affected individuals have at least one of the following: cardiac conduction block, cerebrospinal fluid protein concentration greater than 100 mg/dL, or cerebellar ataxia. Onset is usually in childhood. PEO, characterized by ptosis, paralysis of the extraocular muscles (ophthalmoplegia), and variably severe proximal limb weakness, is relatively benign [53].

g) BCS1L-related disorders: Pathogenic variants in BCS1L are associated with GRACILE (growth restriction, aminoaciduria, cholestasis, iron overload, lactic acidosis, and early death) syndrome, Bjørnstad syndrome (congenital profound hearing loss and pili torti), and an overlapping GRACILE syndrome-Bjørnstad syndrome phenotype. Children with the pure form of Bjørnstad syndrome have normal intellect.

The BCS1L protein is an assembly factor for complex III responsible for insertion of the Fe-S core into the complex. Affected children have a biochemical defect in complex III. The clinical scenario of a hepatoencephalopathy may appear similar to AHS at a single point in time, but mtDNA depletion is not part of the pathology described in those with BCS1L pathogenic variants [54,55].

h) SCO1-related disorders: Hepatic failure and severe encephalopathy have also been associated with biallelic pathogenic variants in SCO1 [56,57].

i) Neuronal ceroid-lipofuscinoses (NCLs): A group of inherited, neurodegenerative, lysosomal storage disorders characterized by progressive mental and motor deterioration, seizures, and early death. Visual loss is a feature of most forms. Phenotypes included in the NCLs that overlap with AHS are CLN1 disease, classic infantile NCL, CLN2 disease, and classic late infantile NCL [58,59].

CLN1 disease: Children with CLN1 disease are normal at birth. Symptoms usually present acutely between ages 6 and 24 months. Initial signs include delayed development, myoclonic jerks and/or seizures, deceleration of head growth, and specific EEG changes. Affected infants develop retinal blindness and seizures by two years of age, followed by progressive mental deterioration. Pathogenic variants in PPT1 can be causative [60].

CLN2 disease: The first symptoms of CLN2 disease typically appear between age 2 and 4 years, usually starting with epilepsy, followed by regression of developmental milestones, dementia, ataxia, and extrapyramidal and pyramidal signs. Visual impairment typically appears between ages 4 and 6 years and rapidly progresses to blindness. Life expectancy ranges from age six years to greater than age 40 years. Pathogenic variants in PPT1, TPP1, CLN5, CLN6, and CLN8 can be causative [61].

j) MERRF: It is a multisystem disorder characterized by myoclonus (often the first symptom) followed by generalized epilepsy, ataxia, weakness, and dementia. Onset is usually in childhood, following normal early development. Common findings are hearing loss, short stature, optic atrophy, and cardiomyopathy with Wolff-Parkinson-White syndrome. Occasionally pigmentary retinopathy and lipomatosis are observed. MERRF is transmitted by maternal inheritance [62].

k) MELAS: It is a multisystem disorder with onset typically occurring in childhood. Early psychomotor development is usually normal. Onset of symptoms is often between 2-10 years. The most common initial symptoms are generalized tonic-clonic seizures, recurrent headaches, anorexia, and recurrent vomiting.

Seizures are often associated with stroke-like episodes of transient hemiparesis or cortical blindness. The cumulative residual effects of the stroke-like episodes gradually impair motor abilities, vision, and mentation, often by adolescence or young adulthood. Sensorineural hearing loss is common. MELAS is transmitted by maternal inheritance [63].

l) Other storage diseases: During infancy and early childhood, when there is history of multi organ involvement and drug resistant epileptiform discharges several mtDNA

disorders such as atypical hexosaminidase A deficiency [64], Sandhoff disease [65], infantile sialidosis [66], and galactosialidosis [67], can be diagnosed by testing for lysosomal enzyme activity in the appropriate tissue.

Discussion

Polymerase gamma-related disorder widely known as POLG related disorder, comprises a spectrum of genetic mitochondrial disorders with overlapping phenotypes. Most common disorders are 1) Alpers syndrome; 2) myoclonic epilepsy myopathy sensory ataxia; 3) ataxia neuropathy spectrum; 4) autosomal recessive progressive external ophthalmoplegia; 5) Childhood myocerebrohepatopathy spectrum; 6) autosomal dominant progressive external ophthalmoplegia. No fixed clinical diagnostic criteria exists, hence diagnosis of the abovementioned disorders is based on clinical suspicion and genetic testing.

Treatment is solely conservative which may include occupational therapy, physical therapy, and speech therapy. Antiepileptic drugs (AEDs) may be used if seizure is a presenting symptom. However, any medications metabolized by hepatic enzymes should be used cautiously to avoid hepatotoxicity. Certain AEDs should not be used because of the risk of developing liver failure [68].

Avoidance of stress, infection, dehydration, fever, and anorexia can de-accelerate acute medical deterioration. Family members and caregivers should be properly educated about symptoms and precipitating factors. Survival of an individual with POLG related disorder largely depends on age at onset, presenting phenotype, and development of any secondary complications.

Conclusion

POLG-related disorders comprise a continuum of overlapping phenotypes that were clinically defined long before their molecular basis was known. Multiorgan system can be involved which can be confused with other storage diseases. Clinicians should bear in mind typical presenting features of each disorder which can aid in diagnosis along with the mutated gene or the enzyme involved. Not much treatment is available at this moment apart from the symptomatic management. More studies are required in future to understand the underlying molecular and pathogenic mechanisms which can be targeted as a primary therapeutic option.

Disclosure

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